Policy Implications of the Changing Epidemiology of Chagas Disease and Stroke

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American trypanosomiasis or Chagas disease (CD) is considered today a global health problem. This parasitic disease, endemic and once almost entirely confined in the Americas for thousands of years, has spread outside Latin America. Economic crisis and population mobility, mainly migration, has spread at first to United States and Canada and later to European countries. Since 2000, increasing numbers of CD cases have been reported in many European countries, including cases among travelers returning from Latin America.

Neurologists should increase their awareness because CD is an important cause of ischemic stroke in endemic regions, which has been also reported among immigrants living in non-endemic countries. The objectives of this article are to review the changing epidemiology of CD in the field of stroke, and to propose some policy implications to raise the awareness, diagnosis, and prevention of this long-term neglected disease.

Epidemiology

Burden of CD in Endemic Countries

CD, a parasitic disease caused by the protozoan Trypanosoma cruzi, is spread from Chile, Argentina, Brazil, Bolivia, Colombia, Venezuela, Caribbean region, Mexico, and southern Texas in the United States. In Latin American endemic countries, CD has been linked to poverty and rural areas and was not considered a public health problem for many years. In fact, the disease is transmitted to humans by the feces of the blood-sucking triatomine bugs through the insect sting (wild vector transmission). Today, CD is endemic in 21 Latin American countries and has become a global health problem because of the migration to developed countries of thousands of asymptomatic or paucisymptomatic T cruzi–infected people who are unaware of their condition.

It is estimated that between 8 and 14 million people are infected with T cruzi in Latin America, including 2 million people infected women of fertile age. Only Brazil has ≥4 million people with the chronic CD infection. Around 20% of the population in endemic countries may be currently living in areas at risk of the disease. However, the true rate of chronic infected people may have been underestimated by policy health makers because many chagasic people do not know they harbor chronic T cruzi infection. The epidemiological pattern of CD has also been modified in endemic regions because of rural-to-urban migration that occurred in the past decades. In urban areas, nonvector transmission occurs through blood transfusion of infected blood, congenital infection, and organ transplantation. In addition, oral transmission outbreaks have been reported in the Amazon basin.

CD is a major cause of chronic cardiomyopathy and ischemic stroke in South America. Most CD acute cases occur in the infancy and are oligosymptomatic, although T cruzi encephalitis may be a severe complication in children. Then an asymptomatic or indeterminate form follows, and may last many years. Nevertheless, it has been estimated that between 30% and 50% of these patients will develop a chronic cardiac (30%), digestive (10%), cardiodigestive (10%) or neurological involvement (unknown percentage) along their life. Chagasic cardiomyopathy is the most common chronic form of the disease and is characterized by progressive myocarditis, heart failure, arrhythmias, conduction disorders, and thromboembolism.

In Latin American countries, the number of annually infected people has been dramatically reduced after the implantation of vector control programs in past decades. Several countries, including Brazil, were declared free of Triatoma infestans vector transmission. At present, the appearance of secondary peridomestic vectors and resistance to insecticides are new recognized difficulties to adequately control the infection in endemic rural areas.

The implementation of compulsory screening for T cruzi infection in most Latin American blood blanks reduced the percentage of blood transfusion–transmitted cases, contributing to a better control of the disease. The rate of congenital transmission via chronically infected mother-to-child is still high and may range from 5.6% in Uruguay to 19% in Northern Chile. Congenital transmission is particularly common in North Argentine and southern Bolivia, a region where 40% of pregnant woman may be infected by T cruzi, and parasitemia is detected in a quarter of infected women.

Global and regional health and economic burden of CD are also high. Globally, the annual burden has been estimated in $627.46 million in healthcare costs and 806.170 disability-adjusted life-years. Global cost has been estimated in $7.19 billion per year and $188.80 billion per lifetime.
Changing Pattern of CD in Nonendemic Countries
In the past 2 decades, the growing migration that flows from Latin American endemic areas to nonendemic countries explains the increased reports of imported CD cases in North America (United States and Canada), European countries, and Western Pacific region (Australia and Japan). Migration of T cruzi–infected patients has spread the disease to nonendemic countries by means of nonvector borne transmission, such as transmission from infected mother to their children and blood transfusion.

The proportion of T cruzi–infected immigrants from endemic countries that are currently living in United States, Canada, or Europe may range between 2% and 5.2%. In United States, ≈2% of 17 million Latin American immigrants were T cruzi infected in 2007, whereas in Canada the 3.5% of ≈157,000 Latin American immigrants are infected. At least 300,000 T cruzi–infected patients may be living in the United States, with 45,000 cardiopathy cases and 300 congenital infections occurring yearly. At least 23 autochthonous chronic T cruzi–infected cases presumably acquired via vector-borne transmission have been reported in the United States, and the estimated prevalence of autochthonous infections is 1 in 354,000 donors. Around 10% of the CD global costs may emanate from United States and Canada. Economic burden of CD may exceed in the United States, a country that has not been traditionally endemic, the cost of Lyme disease ($2.5 billion). In 2008, ≈4 million Latin American immigrants were living in European countries. Spain had received ≈1,678,700 Latin American immigrants by 2008; of these, 5.2% were estimated to be infected with T cruzi.

However, these data may not reflect the true numbers of this neglected disease in nonendemic countries. Official statistics in western countries may not be reliable because illegal or undocumented immigrants have not been included. The data about CD burden may be incomplete because the disease mainly affects the migrated rural poor population from Latin America who have very limited access to diagnosis of CD even in their countries of origin. In the past, the prevalence rates for T cruzi infection in the country of origin were used to calculate the estimated prevalence rate in migration countries; nevertheless, this approach may result in heterogeneous data sources and estimates.

The number of infected cases in Europe probably exceeds 120,000, with >4,300 laboratory-confirmed cases during the past 10 years in Belgium, France, Italy, Spain, Switzerland, and the United Kingdom. The index of underdiagnosis may be very high and ≈95% has not been diagnosed. The proportion of infected T cruzi immigrants detected in Europe is small because most health professionals may not have experience with detection and management of CD nor in the acute stroke setting. The observed low prevalence of CD in some countries that are regular recipients of immigration from endemic regions, such as United Kingdom, Netherlands, or Portugal, also suggests a lack of awareness and official interventions in CD.

Stroke and CD
In Latin America, CD is a major cause of cardioembolic stroke and an independent risk factor for ischemic stroke. In Central Brazil, an epidemiological case-series study detected that ≈20% of 478 consecutively ischemic stroke patients were infected by T cruzi. The risk of stroke seems to be twice as high in chagasic cardiomyopathy as compared with other types of cardiomyopathy, and the frequency of T cruzi infection in acute stroke patients is higher than in acute coronary ones (14% versus 2%).

This epidemiological problem may be even higher because many chagasic patients do not know they are infected by T cruzi. In other Brazilian study, ≈40% of chagasic stroke patients were diagnosed as having CD after presenting with their first stroke. In addition, a positive family history for CD was found in more than two thirds of chagasic stroke patients, and most of them had a history of living in mud houses during childhood.

The presence of apical aneurysm, cardiac arrhythmias, mural thrombus, congestive heart failure, left atrial increased volume, or left ventricle dysfunction are well-known associated risk factors for cardioembolism in CD. Left ventricle apical aneurysm has been detected in ≈40% of CD ischemic stroke patients. Approximately 70% of chagasic stroke patients have ECG abnormalities, including right bundle-branch block (35%), left anterior fascicular block (17%), and atrial fibrillation (15%).

Ischemic stroke may be the first manifestation of CD in patients with mild left ventricle dysfunction, and around one third of chagasic patients who experience an ischemic stroke may have an asymptomatic T cruzi infection. Other noncardioembolic stroke subtypes can occur in asymptomatic T cruzi–infected patients, such as small-vessel infarction and large-vessel atherosclerosis. Asymptomatic T cruzi–infected patients may also have cardiac damage, such as apical aneurysm (27%), left atrial dilatation (12%), or left ventricular hypokinesis (9.4%) and be a source of cardioembolism.

There are few studies that have prospectively evaluated the risk of ischemic stroke in patients with CD. Cases series with 213 CD cardiomyopathy patients followed up on average 36 months showed that the overall incidence of ischemic stroke was 2.7 events per 100 patient-years.

An extensive stroke workup diagnosis is recommended for chagasic stroke patients and should include ECG, Holter monitoring, echocardiogram, carotid echo-Doppler, transcranial Doppler, and a computed tomographic scan or a MRI. Holter monitoring should be used to monitor not only heart frequency, but also atrioventricular blocks and arrhythmias, which have major implications for CD management. Nevertheless, many rural hospitals in South America do not have basic tests and these ancillary examinations are not usually performed.

Impact of Aging on Chagasic Stroke
The South American population is aging, and the percentage of chagasic elderly population will increase in the next decades. Then, an increase of CD cerebrovascular complications is expected in the following years. The prevalence of classical vascular risk factors in chagasic stroke patients seems to be lower as compared with nonchagasic stroke patients. Nevertheless, this fact may be changing because of the aging of the population, the migration from rural to urban areas, and...
the acquisition of more sedentary life habits, obesity, and diabetes mellitus, thus favoring the appearance of mixed type of cardiomyopathies and large-artery disease.

These facts may explain why not all ischemic stroke subtypes observed in CD patients are because of cardioembolism. In fact, internal carotid artery occlusion and critical stenosis have been reported in ≈10% of chagasic patients, and small-vessel disease/lacunar infarctions caused by underlying high blood pressure is increasingly found in *T. cruzi*-infected old people.\(^{15}\)

### Diagnosis

Biological diagnosis of CD is not standardized and in-house tests should be validated. Diagnosis of chronic CD relies on serological methods, such as conventional or recombinant ELISA, indirect hemagglutination assay, and indirect immunofluorescence assay. A commercially available confirmatory assay to confirm the results of the screening/diagnostic tests is needed. Real-time polymerase chain reaction is the most sensitive tool to diagnose acute and early congenital CD. It may also detect low parasitemia burden in patients with chronic CD.\(^{3}\) However, this technique needs to be further validated because high differences in median parasitemia measured by polymerase chain reaction was found in samples of chronic chagasic patients from different countries. Variations in parasite burden may also be caused by *T. cruzi* genetic diversity. Differences in *T. cruzi* strains might be another factor to explain the different clinical presentations of the disease and influence parasite levels in infected individuals from different regions of Latin America.\(^{2}\)

Table 1 summarizes a checklist when suspecting a case of CD in an acute stroke patient in the clinical setting.

### Prognosis

CD usually causes large total or partial anterior circulation infarctions affecting the middle cerebral artery in >80% of cases.\(^{15}\) The true prevalence of CD in acute stroke patients is unknown in endemic countries (CD serology is not routinely performed in all stroke patients), and the true data about mortality in acute chagasic ischemic stroke are unknown. Even more, the absence of stroke units in many large Latin American hospitals is other factor that limits adequate therapy and follow-up.

Chagasic patients may have a double risk of death from stroke than nonchagasic stroke patients. In the Bambui study, the 10-year cumulative incidence of death from stroke among *T. cruzi*-infected patients and noninfected subjects was 4.8% and 2.3%, respectively. High brain natriuretic peptide levels and atrial fibrillation increased the risk of death from stroke by 11.5-fold.\(^{30}\)

The reported date about global mortality in chronic CD (≈4%) seems to be far from the true data, as many studies have only taken into account sudden death (60% of causes), heart failure (30%), and thromboembolism (19%), and did not include acute chagasic stroke patients.\(^{19}\) In fact, pulmonary and cerebral embolism could be the third most common cause of death in CD after fatal arrhythmias and progressive heart failure.\(^{2}\) Factors associated with an increased mortality rate include congestive heart failure, cardiomegaly, left ventricle systolic dysfunction, nonsustained ventricle tachycardia, and male sex.\(^{30}\) In addition, poverty and low social and economic conditions have been associated with worse outcome, and the use of oral anticoagulation as preventative medication may be difficult in poor rural regions without access to the health system.\(^{3}\)

### Evidence-Based Treatment in Chagasic Stroke

There are only 2 available trypanocide drugs, nifurtimox and benznidazole, that are indicated to treat CD in the acute stage and during reactivation. Side effects are frequent, and these drugs have not proven clear efficacy during the chronic form of the disease.\(^{3}\) Traditionally, the low public health priority about this forgotten tropical disease may explain the virtually absence of clinical trials and the development of new drugs to treat the disease. Results from the Benznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) clinical trial is expected to know whether this drug may be effective to treat those patients with chronic chagasic cardiomyopathy.\(^{30}\)

The efficacy and safety of pharmacological interventions for treating acute stroke and preventing the recurrence of chagasic ischemic stroke needs further elucidation. Randomized clinical trials in chagasic stroke and chronic chagasic cardiomyopathy are needed and they should provide evidence of a treatment effect.

The experience with the use of thrombolytic therapy in CD stroke patients that harbor an apical aneurysm or a mural thrombus is very limited, although some case reports have described a safe thrombolytic treatment in acute chagasic stroke within 3 hours of onset.\(^{21}\) Nevertheless, safety of thrombolytic therapy still needs to be further elucidated in acute CD stroke patients affected by an apical aneurysm or mural thrombus because recurrent stroke after thrombolytic therapy has been described in some patients with preexisting intracardiac thrombus.
Prevention Strategies
More than 20% of CD stroke patients may experience a recurrent stroke, and the implementation of prevention strategies is indeed necessary.\textsuperscript{15} Secondary prevention with oral long-term anticoagulation has been recommended in chagasic stroke patients who have an additional cardioembolic factor, such as atrial fibrillation, apical aneurysm, mural thrombus, ventricle arrhythmia, or severe heart failure.\textsuperscript{2} However, no clinical trials have been conducted to demonstrate the higher efficacy of anticoagulation against antiplatelet therapy in the secondary prevention of stroke in CD. Even more the efficacy of trypanocidal treatment and specific antiplatelet therapy in chagasic stroke patients has not been properly assessed in clinical trials. This fact is even more urgent in the case of those chagasic patients who experience a stroke and do not have any associated cardiac structural damage.

As many of these patients experience large ischemic stroke, long-term rehabilitation is also needed. Nevertheless, rehabilitation programs and even home and support rehabilitation programs are scarce in many Latin American countries. So, specific multidisciplinary teams should be performed to collaborate and treat severe sequel and dependence in the activities of daily living after stroke in CD.

Implications for Policy Makers

Recommendations for policymakers in endemic countries should include CD educational, research and training programs, awareness and active detection programs in the clinical setting, and public health programs to avoid transmission in the community (Table 2).

The screening of all people experiencing an acute stroke in endemic countries may provide useful information for health policy makers. Screening for CD in Latin American stroke patients seems to be more relevant as many CD are asymptomatic at the time of stroke onset.\textsuperscript{16} Active programs to detect family members affected by CD should be implemented in endemic countries because more than half of chagasic stroke patients may have ≥1 relative affected by CD.\textsuperscript{3} When a stroke patient is diagnosed as having CD, the health team should contact family members and perform serological testing to detect asymptomatic CD cases.

In both endemic and nonendemic countries, health professionals, including neurologists, may be unaware about CD and have not been trained in the diagnosis of the disease. So, they may not have standardized protocols to diagnose CD when a patient experiences a stroke. Neurologists should be trained in the differential diagnosis of CD as a cause of stroke and perform routinely serological antibodies for CD in all ischemic stroke patients in endemic countries, and also in all Latin American origin patients who experience an acute stroke in nonendemic countries.

The screening for CD in nonendemic countries should also be considered for those patients who were born in endemic countries, and also in travelers who lived for >6 months in endemic areas. The different pattern of accessibility and the use of health services, the presence of socioeconomic and cultural constraints, and lack of information in immigrants may limit their interaction with western healthcare systems.\textsuperscript{22} So, health workers and anthropologists should identify access barriers to medical assistance to reduce inequality in the use of health services that may limit the effectiveness of any intervention in chagasic immigrants in nonendemic countries.

Health policy makers should implement strategies to uniformly prevent donation of blood and organ from \textit{T. cruzi}–infected donors in endemic countries. Some of these organ donors may have died because of sudden death or large stroke without being diagnosed as having a \textit{T. cruzi} chronic infection. Public health programs are also needed to assure early detection and treatment for the congenital and chronic cases of CD in endemic countries. Because of the increased number of imported cases, some European countries are developing strategies to control the spread of the infection though blood transfusions and organ transplantation.\textsuperscript{8} However, from a global public health point of view, the uniform implantation of these strategies is urged in endemic countries and also in nonendemic countries that are receiving immigrants from endemic areas.

<table>
<thead>
<tr>
<th>Table 2. Recommendations for Policymakers About Chagas Disease</th>
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<tbody>
<tr>
<td><strong>Applied research</strong></td>
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<tr>
<td>Create multicenter/national database on chagasic patients</td>
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<td>Potentiate basic research and pathological studies about CD</td>
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<td>Potentiate the study of biomarkers associated with higher risk of chronic involvement in CD</td>
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<td>Perform epidemiological studies about CD by \textit{T. cruzi} strains and geographical areas</td>
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<td>Develop clinical trials about new, more effective and less toxic, trypanocide drugs. Explore combination of trypanocide drugs</td>
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<td>Develop consensus guidelines on diagnosis and treatment of CD</td>
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<tr>
<td><strong>Clinical setting</strong></td>
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<tr>
<td>Screening for \textit{T. cruzi} among ischemic stroke patients from endemic regions</td>
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<tr>
<td>Standardization of follow-up among chronic CD patients</td>
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<tr>
<td>Active surveillance programs among asymptomatic \textit{T. cruzi}–infected patients</td>
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<tr>
<td>Standardization of diagnostic serological and PCR techniques</td>
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<tr>
<td>Development of prevention programs for chagasic stroke</td>
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<tr>
<td>Detection of \textit{T. cruzi} drug resistance</td>
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<td><strong>Public health</strong></td>
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<td>Develop a surveillance system to report detected cases of CD</td>
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<tr>
<td>Measures to prevent congenital and blood \textit{T. cruzi} transmission. Compulsory serological tests in blood banks</td>
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<tr>
<td>Develop active screening programs for \textit{T. cruzi} detection in stroke patients from endemic areas and their family members</td>
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<tr>
<td>Potentiate awareness campaigns in the community, schools, and risk groups about CD</td>
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<tr>
<td>Promote diagnosis, treatment, prevention, and rehabilitation strategies for CD in both endemic and nonendemic countries</td>
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<tr>
<td><strong>Teaching/training</strong></td>
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<td>Training health workers and neurologists on early diagnose of CD and chagasic stroke</td>
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<tr>
<td>Development of pre and postgraduation training programs in Tropical Neurology</td>
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CD indicates Chagas disease; PCR, polymerase chain reaction; and \textit{T. cruzi}, \textit{Trypanosome cruzi}. |
Adequate training programs in Tropical Neurology for neurologists and other health professionals should be performed to improve their awareness about CD. However, academic and clinic centers specialized in Tropical Neurology are scarce. Teaching and training programs in Tropical Neurology at the level of pre- and post graduation should be implemented in both endemic and western countries to detect and early diagnose other tropical causes of stroke, such as dengue, malaria, or gnathostomiasis.

The development of clinical trials are urgently needed to evaluate the efficacy and safety of thrombolytic therapy and other therapies in the acute chagasic stroke and also to assess the best prevention strategies with anticoagulation/antiplatelet therapy in chagasic stroke subtypes.

Conclusions
A surveillance system should be created to report the true prevalence of CD and chagasic stroke in both endemic and non-endemic countries. The systematic screening for CD should be considered in all stroke patients from endemic regions and in immigrants from endemic regions that experience a stroke in nonendemic countries. Strategies for early diagnosis, standardized follow-up, prevention of stroke recurrence, and the development of new clinical trials for the acute stroke treatment and prevention in CD are encouraged. Diagnosis and treatment of chagasic stroke should also cover high-risk groups, including poor and undocumented immigrants from endemic countries. The training of neurologists, health workers, and pre- and postgraduation students about CD is needed.

The teaching and training in Tropical Neurology should be reinforced by means of comprehensive programs that covered emerging tropical diseases.

Disclosures
None.

References

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